Evaluation of the utility of localized adjuvant radiation for node-negative primary cutaneous squamous cell carcinoma with clear histologic margins

Emily Stamell Ruiz, MD, MPH[*]; Shlomo A. Koyfman, MD[†]; Syril Keena T. Que, MD, MPH[“]; Jason Kass, MD, PhD[‡]; Chrysalyne D. Schmults, MD, MSCE[*]

[*]*Department of Dermatology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA*
[“]*Department of Dermatology, Indiana University School of Medicine, Indianapolis, IN*
[†]*Department of Radiation Oncology, Cleveland Clinic, Cleveland, OH*
[‡]*Department of Otolaryngology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA*

Manuscript Word Count: 2,615
Abstract Word Count: 222
Capsule Summary Word Count: 50
Tables: 5
Figures: 0
References: 23

Funding Sources: Dr. Ruiz is supported by a Dermatology Foundation Career Development Award.

IRB approval status: Approved by the Partners Human Research Office.

Conflicts of Interest: None declared.

Reprint requests: Chrysalyne Schmults

Corresponding Author:
Chrysalyne D. Schmults, MD, MSCE
Department of Dermatology, Brigham and Women's Hospital
1153 Centre Street Suite 4J, Boston, MA 02130
Tel.: 617-983-4626 | Fax: 617-983-4504 | Email: cschmults@partners.org

Abbreviations:

AJCC	American Joint Committee on Cancer
BWH	Brigham and Women's Hospital
CCPDMA	Complete Circumferential Peripheral and Deep Margin Assessment
CSCC	Cutaneous Squamous Cell Carcinoma
DM	Distant Metastasis
DSD	Disease-Specific Death
LCNI	Large Caliber Nerve Invasion
LR	Local Recurrence
LVI	Lymphovascular Invasion
MMS	Mohs Micrographic Surgery
NCCN	National Comprehensive Cancer Network
NM	Nodal Metastasis
PNI	Perineural Invasion
S+ART	Surgery and Adjuvant Radiation
SM	Surgery Monotherapy

Abstract

Background: Though NCCN recommends consideration of localized adjuvant radiation following clear-margin surgery for cutaneous squamous cell carcinoma (CSCC) with large caliber (≥0.1mm) nerve invasion (LCNI) and other high-risk features, only a single small study has compared surgery plus adjuvant radiation (S+ART) to surgical monotherapy (SM) for CSCC.

Objectives: Compare surgery plus adjuvant radiation (S+ART) to surgical monotherapy (SM) for primary CSCCs with LCNI and other risk factors.

Methods: Matched retrospective cohort study of primary CSCCs (matched on gender, age, immune status, type of surgery, diameter, differentiation, depth and LCNI) treated with S+ART versus SM. Subgroup analysis of CSCCs with LCNI was performed.

Results: 62 CSCCs were included in matched analysis (S + ART: 31, SM: 31) and 33 in LCNI analysis (S+ART: 16, SM: 17). There was no significant difference in local recurrence (LR), metastasis, or death from disease in either analysis. Risk of LR was low (7, 8%) with 3 of the LRs being effectively treated upon recurrence.

Limitations: Single academic center, non-randomized design.

Conclusion: Adjuvant radiation did not improve outcomes compared to SM due to a low baseline risk of recurrence; although ART for named nerve invasion and LCNI of 3 or more nerves has been shown to improve outcomes in a prior study. Randomized studies are needed to define the subset of CSCC for whom adjuvant radiation has utility.

Introduction

Approximately 3.7-5.2% of CSCCs will develop metastasis and 2-3.5% of patients will die from disease.[1-4] While the primary treatment of high-risk tumors is surgical removal with complete circumferential peripheral and deep margin assessment (CCPDMA), adjuvant therapies are sometimes considered in cases thought to have a risk of recurrence or death.[5] Adjuvant radiation (ART) is sometimes used following surgery with clear histologic margins for select cases of CSCC. The National Comprehensive Cancer Network (NCCN) includes ART as a consideration for margin-negative CSCCs with extensive, large (nerve caliber ≥0.1mm), or named-nerve involvement or if other high-risk features are present at the clinician's discretion.[5]

Despite these recommendations, data on the efficacy of ART for margin-negative CSCCs is limited. Prior studies have focused on CSCCs with perineural invasion (PNI); however, the majority do not compare radiation outcomes to tumors treated with surgery monotherapy (SM) and so the effect of radiation is difficult to quantify.[6-11] One prior study of 102 tumors that compared S+ART to SM found longer recurrence- (94% vs. 25%, p=0.01) and disease-free (73% vs. 40%, p=0.05) 2-year survival in tumors with PNI of more than 2 nerves (n=30), respectively, but there was no difference in cases with PNI of 1-2 nerves.[12] Whether tumors had clear surgical margins prior to radiation was not specified.

Data on ART for high-risk CSCCs without PNI is very heterogenous due to lack of consensus on the definition of high-risk CSCC. A 2009 systematic review was unable to draw conclusions about ART efficacy due to insufficient data.[13] A more recent analysis evaluated local recurrence (LR) following ART for 52 high-risk CSCCs with depth of invasion > 6mm or desmoplasia. While the study excluded gross residual tumor post-surgery, it included tumors with histologically positive margins (n=16). LR-free survival was 96% (95% confidence interval, 90-100%) at 2 years but there was no SM group for comparison.[14]

Radiation therapy is associated with morbidity, high-cost, and can complicate future attempts at resection should recurrence occur. Thus, data evaluating its impact on outcomes in the adjuvant setting for node-negative CSCC is needed in order to utilize radiation appropriately. The aim of this study was to perform a matched analysis of the impact of ART on completely-resected primary CSCC. Since large-caliber (≥0.1mm in caliber) nerve invasion (LCNI) is an indication to consider ART per NCCN guidelines and there is data to support improved outcomes in tumors with LCNI, but not small caliber PNI,[5,12] a subgroup analysis of cases with LCNI was also performed utilizing controls without PNI.

Methods

Data Collection

The study was approved by Partners Human Research Committee. Patients with CSCC diagnosed at Brigham and Women's Hospital (BWH) from 1/1/2000-12/31/2017 were identified via department of pathology electronic database. Pathology reports were reviewed and

noncutaneous SCC, anogenital SCC, in situ CSCC, and recurrent CSCC were excluded. Medical records of all eligible patients were reviewed for primary tumor data, outcome data [including local recurrence (LR), nodal metastasis (NM), distant metastasis (DM), and disease-specific death (DSD)], and types of treatment performed (including surgical approach and adjuvant therapy). Cases that received localized radiation underwent additional chart review for the following information: radiation modality, dose, fractions, dates that treatment was performed, and reason for ART. Only primary tumors with clear histologic margins following surgical excision (either wide local excision or Mohs micrographic surgery (MMS)) were included.

Matched Analysis

Primary tumors treated with surgical excision with clear surgical margins and ART (S+ART) were identified. Exact matching was used to select tumors treated with surgical excision monotherapy with clear surgical margins (SM). Case pairs were matched on gender, age (+/- 10 years), immune status, type of surgical treatment, diameter (≥ 2cm vs. <2cm), differentiation (poor vs. well or moderate), depth of invasion (beyond subcutaneous fat vs. dermis/subcutaneous fat), and LCNI (present vs. absent). Tumors where controls could not be identified were excluded from analysis.

Large Caliber Nerve Invasion (LCNI) Analysis

Since LCNI is the most common indication for ART and a number of these tumors treated with ART could not be matched due to the strict matching criteria, LCNI tumors were analyzed separately. All primary LCNI tumors with surgically clear margins were included in this

analysis, stratified by whether ART was used (including 6 cases contained in the matched analysis above).

Statistical Analyses

Patient and tumor characteristics were analyzed using descriptive statistics and frequency tabulation. For the matched analysis, outcomes of interest were analyzed by tumor pair and McNemar's Test was used to determine whether there was a difference in LR, NM, DM. For the LCNI cohort analysis, Chi-square and Fisher's exact tests were used to determine whether there was a difference in LR, NM, DM, and DSD. Multivariable and survival analyses were not performed due to small number of outcomes and lack of significance on univariate analysis.

All reported *p*-values were two-sided with type I error (α) of <0.05 considered to be statistically significant. Statistical analyses were performed using Stata version 14.0 (StataCorp, College Station, TX).

Results

Matched Case Analysis

Forty-one CSCCs treated with surgical excision with clear margins and ART were identified of which 31 were able to be matched to similar cases as per criteria described in methods (table 1). There was no statistical difference in gender, age, immune status, diameter, depth of invasion, large caliber PNI, differentiation, type of surgical treatment (i.e. excision vs. MMS), and tumor location in S+ART vs. SM groups. Details on the patient and tumor risk factors for cases in the S+ART group are included in table 5. Although it did not meet statistical significance, more

tumors in the radiation group had lymphovascular invasion (LVI; S+ART 4 (13%) vs. SM 1 (3%), p=0.4). There was a statistically significant difference in median follow-up time (S+ART 49.5 (SD 32.8) vs. SM 32.9 (SD 27.3), p=0.03). Based on the American Joint Committee on Cancer (AJCC) 8th edition staging system for CSCC of the head and neck, there was no difference in tumor stages. The majority of tumors in both groups were BWH T2b (S+ART 20 (65%) vs. SM 21 (68%)).

In the S+ART group, the reason for radiation included perineural invasion (9, 29%), multifocal infiltrative tumor (9, 29%), deeply invasive tumor to bone, cartilage, parotid, or fascia (8, 26%), lymphovascular invasion (4, 13%), and no epidermal connection (1, 3%). Details of the radiation treatment were available for 28 (90%) patients with all receiving localized radiation only. Twenty-seven (96%) patients completed their planned radiation treatment which ranged from 39-70 Gy total. Three patients received chemoradiation consisting of cisplatin (dose not available) in 1 patient. The other two received carboplatin 1-1.5auc + paclitaxel 30mg/m^2 for 2 and 4 weeks during the course of ART. One of the patients discontinued the chemotherapy due to hospitalization and one switched to cetuximab 250mg/m^2 for 1 week due to pancytopenia. In terms of acute radiation toxicities, most patients experienced grade 1 or 2 skin erythema. One (3%) experienced grade 3 skin erythema and 4 (13%) experienced grade 1 or 2 mucositis. Two patients developed late radiation toxicities; 1 (3%) had recurrent cellulitis and 1 (3%) had chronic pain.

Clinical outcomes for the matched-case analysis are shown in table 3. A total of 4 tumors developed poor outcomes (LR (1), NM (1), LR+DSD (1), LR+DM+DSD (1)). There was no

difference in LR (S+ART 3 (10%) vs. SM 1 (3%), p=0.3), NM (S+ART 1 (3%) vs. SM 0 (0), p=0.3), DM (S+ART 1 (3%) vs. SM 0 (0), p=0.3), and DSD (S+ART 2 (6%) vs. SM 0 (0), p=0.2). Of the 3 LRs in the S+ART cohort, 1 was treated with MMS and had no further recurrences after 84 months of follow up, 1 patient developed an inoperable recurrence on the scalp and died of local disease 6 weeks after diagnosis of the recurrence, and 1 patient developed an LRs on the scalp as well as in transit metastases, NM, and DM and died of disease 5 months after diagnosis of the recurrence. The LR in the SM cohort was treated with a WLE with a positive deep margin and salvage radiation. The patient developed NM and DM 9 months later and died of disease 11 months after diagnosis of the recurrence. Of note, one patient in the S+ART group died from a second primary CSCC (not part of the study) diagnosed 6 years after the study tumor and did not receive radiation. The study tumor had no evidence of recurrence 81 months after diagnosis when the patient died of the other CSCC so the study tumor was recorded as no LR, NM, or DSD.

LCNI Analysis

Thirty-three tumors were included in the LCNI analysis, of which 16 (48%) received S+ART and 17 underwent SM (52%) (table 2). There was no difference in follow up time, immunosuppression, tumor location, tumor diameter, depth of invasion, histologic differentiation, LVI, primary tumor treatment, adjuvant chemotherapy, or AJCC 8 tumor stage. The SM was 10 years older and 40% more male than the S+ART group, though these were not statistically significant differences between the groups. There was a statistically significant difference in tumor stage by the BWH staging system with low stage tumors (BWH T2a)

comprising 41% of the SM group and 0% of the S+ART group (p=0.01). Thus, all cases in the S+ART group had another prognostic risk factor besides LCNI.

Table 3 includes the clinical outcomes for the LCNI analysis based on treatment. A total of 3 tumors developed poor outcomes (LR (2), LR+DSD (1)). Although there was no statistically significant difference in any outcome, more cases in the SM group had LRs [S+ART 0 (0) vs. SM 3 (18%), p=0.2)]. One of the 3 patients developed multiple in transit metastases treated with excision and ART, with no evidence of recurrence at 9 months. The second patient developed a LR requiring orbital exenteration. A second recurrence was treated with palliative radiation, and resulted in death shortly thereafter. The final patient had a LR successfully treated with MMS with no evidence of recurrence 36 months later.

Description of Cases with Poor Outcomes

Table 4 summarizes the characteristics and outcomes of the cases with poor outcomes in both the matched case and LCNI analyses.

Discussion

To the best of our knowledge, this study is the first to compare S+ART to SM for node-negative primary CSCCs with clear surgical margins, the second for cases with PNI, the first for cases with LCNI, and the first to conduct a matched analysis of multiple prognostic factors. There was no difference in outcomes in either the matched-case or LCNI analyses. The results are in keeping with the other study of PNI in that a (non-significant) trend was found for less LR in cases with significant (large-caliber) PNI treated with ART. However, 2 of the 3 LRs in the SM

group accounting for the trend were effectively treated at the time of LR. In the 89 total cases reported herein, only 7 (8%) had a local recurrence, of which 3 were successfully salvaged at the time of LR. The null findings herein reflect a low baseline risk of poor outcomes for high-stage primary CSCCs with clear histologic margins. Even when LR occurs, most patients still appear to be curable. Although this is a small study, a post-hoc power analysis shows that the matched analysis was adequately powered to detect a 50% reduction in LR, the effect of ART on recurrence rates in epithelioid tumors, since the sample size needed is 53 total tumors and the analysis include 62 tumors. The LCNI analysis was powered to detect a 60% reduction, so a larger study is needed to assess smaller reductions.

Margin status following surgery greatly impacts outcomes. CCPDMA (en face sectioning with nearly 100% margin assessment, e.g. Mohs excision) is recommended by the NCCN for high-risk CSCCs (as is wide excision if it can be closed primarily).[15] A systematic review comparing standard assessment (approximately 1% of margin histologically evaluated) to CCPDMA found a higher risk of recurrence for keratinocytic carcinomas with PNI treated with standard assessment (23%) versus CCPDMA (10%, p=0.0004).[16] A recent study of 647 CSCCs treated with only MMS found that 10%, 17%, 5%, and 5% of 145 high-stage CSCCs (defined as BWH T2b/T3) the risk of LR was only 10%.[17] ART for epithelial tumors is offered when the risk of recurrence exceeds 15-20%. Since radiation is not expected to impact nodal or distant metastasis, a 10% LR risk for high-stage CSCC may not be high enough for radiation to significantly impact recurrence risk.

It is possible that if a subset of CSCCs with a greater risk of LR were identified, radiation may be better able to influence outcomes. Meanwhile, since the risk of poor outcomes is elevated for high-stage CSCC, it is reasonable to monitor such tumors with close clinical and radiologic surveillance.[18,19] Though the data presented herein do not support ART solely on the basis of PNI, none of the cases had named nerve and extensive PNI was not routinely recorded given the lack of a clear definition. Therefore, it is possible that ART may impact outcomes with more extensive nerve invasion. Currently in our practice, we utilize ART for named nerve invasion, LCNI with 3 or more nerves, as supported by the single comparative study of more advanced PNI,[12] or when clear surgical margins are in question. A multidisciplinary discussion is recommended for very aggressive or recurrent tumors in order to select cases that may benefit from adjuvant treatment.

Despite the findings presented herein, it is important to recognize that there is good evidence to support radiation for node-positive CSCCs. A retrospective study of 122 patients with CSCCs metastatic to cervical lymph nodes found improved 5-year disease free survival (74% vs. 34%, p=0.001) and 5-year overall survival (66% vs. 27%, p=0.003) in patients who underwent surgery and radiation compared to surgery alone.[20] Another study found lower locoregional recurrence (20% vs. 43%, p values not reported) and improved 5-year disease-free survival rate (73% vs. 54%; p=0.004) in 167 patients with metastatic CSCC of the head and neck (including parotid metastases) who received S+ART versus SM, respectively.[21]

This study is subject to limitations. In the matched-case analysis, the shorter mean follow-up time in SM group (SM 33 months vs. S+ART 49 months) could underestimated the risk of

poor outcomes. However, average follow up time was more than 2 years and 85-96% of recurrences occur within 2 years of treatment, so the impact of the differential follow-up was likely minimal.[12,22] Since the study is retrospective, there were no standard inclusion criteria for tumors receiving ART. However, the cohort reflects current clinical scenarios where ART is utilized in CSCC. Radiation treatment fields were not reviewed and there was variation in treatment protocols. However, in the matched analysis there was only 1 LR in the SM group indicating surgery alone may be sufficient, which would make variation in radiation protocols a moot point. In the LCNI analysis, those in the surgical monotherapy group were 10 years older and 40% more male (both are factors associated with worse CSCC outcomes).[23] However, this group also had lower stage disease (41% were BWH low-stage vs none in ART group). Such differences likely balanced each other and are unlikely to be responsible for the lack of difference seen between treatment groups.

Conclusion

ART for node- and margin-negative primary CSCC did not improve outcomes compared to SM, due to low baseline risk of poor outcomes in primary CSCCs with clear histologic margins. The 18% local recurrence risk in LCNI cases treated with SM is relatively high, but represents only 3 cases of recurrence, 2 of which were successfully treated at time of recurrence. Randomized trials are needed to define which CSCC patients benefit from ART. Meanwhile, the present study represents the only comparative study of ART versus SM for node- and margin-negative CSCCs.

Acknowledgements:

We thank Jonathan D. Schoenfeld, MD, MPhil, MPH of the Department of Radiation Oncology, Dana-Farber Cancer Institute for assisting us in the radiation treatment content and Anita Giobbie-Hurder of the Division of Biostatistics, Dana-Farber Cancer Institute for statistical counseling.

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Table 1. Baseline characteristics of cases in the matched-case analysis

Characteristics	Surgical monotherapy (n=31)	Surgery + ART (n=31)	p-value*
Age at diagnosis, mean (SD), y	73.9 (11.9)	69.1 (12.8)	0.1†
Follow-up time, median (IQR), months	32.9 (27.3)	49.5 (32.8)	0.03†
Sex, n (%)			
Female	9 (29)	9 (29)	1.0
Male	22 (71)	22 (71)	
Immunosuppression, n (%)			
No	18 (58)	21 (68)	0.6
Yes	13 (42)	10 (32)	
Tumor location, n (%)			
Ear and lip	5 (16)	7 (23)	0.6
Head and neck	19 (61)	18 (58)	
Trunk	4 (13)	4 (13)	
Arms, hands, legs, feet	3 (10)	2 (6)	
Tumor diameter			
<2.0 cm	12 (39)	12 (39)	1.0
≥2.0 cm	19 (61)	19 (61)	
Depth of invasion			
Dermis/Subcutaneous fat	14 (45)	14 (45)	1.0
Beyond Subcutaneous fat	17 (55)	17 (55)	
Histologic differentiation			
Well and moderate	15 (48)	15 (48)	1.0
Poor	16 (52)	16 (52)	
Perineural invasion			
No	20 (65)	13 (42)	0.1
Yes	11 (35)	18 (58)	
Diameter of perineural invasion			
<0.1 mm or no perineural invasion	25 (81)	25 (81)	1.0
≥0.1 mm	6 (19)	6 (19)	
LVI			
No	30 (97)	27 (87)	0.4
Yes	1 (3)	4 (13)	
Primary treatment, n (%)			
Surgical excision	9 (29)	10 (32)	1.0
Mohs surgery	22 (71)	21 (68)	
Adjuvant chemotherapy			
No	31 (100)	28 (90)	0.2‡
Yes	0 (0)	3 (10)	
AJCC-8 tumor stage			
T1	5 (16)	3 (10)	0.9
T2	2 (6)	1 (3)	
T3	16 (52)	20 (65)	
T4	1 (3)	1 (3)	
Not applicable§	7 (23)	6 (19)	

BWH tumor stage			
T1	0 (0)	0 (0)	
T2a	9 (29)	7 (23)	0.4
T2b	21 (68)	20 (65)	
T3	1 (3)	4 (13)	
Indication for ART			
Perineural invasion	-	9 (29)	NA
Multifocal infiltrative Tumor	-	9 (29)	
Deeply invasive to bone, cartilage, parotid, or fascia	-	8 (26)	
Lyphovascular invasion	-	4 (13)	
No epidermal connection	-	1 (3)	

AJCC, American Joint Committee on Cancer; BWH, Brigham and Women's Hospital; SD, standard deviation; ART, adjuvant radiation therapy.

[*]Chi-square statistics unless otherwise specified

[§]AJCC-8 staging only applies to CSCC on the head and neck. "Not applicable" indicates tumors on non-head and neck locations.

[†]Student t-test p-value

[‡]Fisher exact test p-value

Table 2. Baseline characteristics of cases with large caliber nerve invasion (LCNI)

Characteristics	Surgical monotherapy (n=17)	Surgery + ART (n=16)	p-value*
Age at diagnosis, mean (SD), y	73.5 (15.2)	63.8 (16.7)	0.09†
Follow-up time, median (IQR), months	27.3 (21.6)	43.3 (30.9)	0.09†
Sex, n (%)			
Female	5 (29)	9 (56)	0.2
Male	12 (71)	7 (44)	
Immunosuppression, n (%)			
No	9 (53)	11 (69)	0.5
Yes	8 (47)	5 (31)	
Tumor location, n (%)			
Ear and lip	1 (6)	4 (25)	0.5
Head and neck	12 (71)	10 (63)	
Trunk	2 (12)	1 (6)	
Arms, hands, legs, feet	2 (12)	1 (6)	
Tumor diameter			
<2.0 cm	12 (71)	8 (50)	0.3
≥2.0 cm	5 (29)	8 (50)	
Depth of invasion			
Dermis/Subcutaneous fat	9 (53)	7 (44)	0.7
Beyond Subcutaneous fat	8 (47)	9 (56)	
Histologic differentiation			
Well and moderate	16 (94)	12 (75)	0.2
Poor	1 (6)	4 (25)	
LVI			
No	17 (100)	16 (100)	1.0
Yes	0 (0)	0 (0)	
Primary treatment, n (%)			
Surgical excision	0 (0)	0 (0)	1.0
Mohs surgery	17 (100)	16 (100)	
Adjuvant chemotherapy			
No	17 (100)	16 (100)	1.0‡
Yes	0 (0)	0 (0)	
AJCC-8 tumor stage			
T1	0 (0)	0 (0)	0.7
T2	0 (0)	0 (0)	
T3	13 (76)	14 (88)	
T4	0 (0)	0 (0)	
Not applicable§	4 (24)	2 (12)	
BWH tumor stage			
T1	0 (0)	0 (0)	
T2a	7 (41)	0 (0)	0.01
T2b	10 (59)	15 (94)	
T3	0 (0)	1 (6)	

AJCC, American Joint Committee on Cancer; BWH, Brigham and Women's Hospital; SD, standard deviation; PNI, perineural invasion; ART, adjuvant radiation therapy

[*]Chi-square statistics unless otherwise specified

[§]AJCC-8 staging only applies to CSCC on the head and neck. "Not applicable" indicates tumors on non-head and neck locations.

[†]Student t-test p-value

[‡]Fisher exact test p-value

Table 3. Clinical outcomes

Matched-Case Tumors			
	Surgical monotherapy (n=31)	**Surgery + ART (n=31)**	**p-value***
Local recurrence, n (%)	1 (3)	3 (10)	0.3
Nodal metastases, n (%)	0 (0)	1 (3)	0.3
Distant metastases, n (%)	0 (0)	1 (3)	0.3
Disease-specific death, n (%)	0 (0)	2 (6)	0.2
Large Caliber PNI Tumors			
	Surgical monotherapy (n=17)	**Surgery + ART (n=16)**	**p-value†**
Local recurrence, n (%)	3 (18)	0 (0)	0.2
Nodal metastases, n (%)	0 (0)	0 (0)	1.0
Distant metastases, n (%)	0 (0)	0 (0)	1.0
Disease-specific death, n (%)	1 (6)	0 (0)	1.0

Abbreviations: ART, adjuvant radiation therapy; PNI, perineural invasion
*p-value determined using McNemar's Test
†p-value determined using Fisher's Exact Test

Table 4. Characteristics and outcomes of cases from the matched-case and LCNI analyses which developed a poor outcome.

Case #	Clinical History	Tumor Location	Tumor Stage (BWH/AJCC 8)	High-Risk Factors	Primary Tumor Treatment	Outcomes	Disease Free Survival (months)
Poor Outcomes from Case-Control Analysis							
1	82-year-old M Diffuse large T cell lymphoma	Cheek	T2B/T3	Poor-Differentiation Tumor Diameter (3.0cm) Depth of invasion (fascia)	MMS	LR	3
Matched Case Treated with S+ART	75-year-old M CLL	Scalp	T3/T3	Poor-Differentiation Tumor Diameter (4.0cm) Depth of invasion (bone)	MMS ART with electrons (55Gy in 20 fractions)		81
2	42-year-old M Kidney Transplant	Cheek	T2B/T3	Tumor Diameter (4.0cm) Depth of Invasion (Parotid)	MMS ART (60Gy in 30 fractions)	LR	8
Matched Case Treated with SM	64-year-old M Lung Transplant	Ear	T2B/T3	Tumor Diameter (2.5cm) Depth of Invasion (Perichondrium)	MMS		69
3	74-year-old M Lung Transplant	Scalp	T2B/T3	Poor-Differentiation Depth of Invasion (fascia) LVI	MMS ART with electrons (60Gy in 30 fractions)	LR DM DSD	5
Matched Case Treated with SM	77-year-old M	Scalp	T2B/T3	Poor-Differentiation Depth of Invasion (Fascia)	MMS		25
4	74-year-old M	Scalp	T3/T4A	Tumor Diameter (4.0cm) Depth of Invasion (Bone)	Excision ART Adjuvant Chemotherapy	LR DSD	17
Matched Case Treated with SM	73-year-old M	Forehead	T2B/T3	Tumor Diameter (2.3cm) Depth of Invasion (Muscle)	MMS		20
Poor Outcomes from Large Caliber PNI Analysis							
6	80-year-old M Kidney Transplant	Medial Canthus	T2B/T3	Depth of Invasion (Muscle) Large-Caliber PNI	MMS	LR DSD	3
7	58-year-old M Lung Transplant	Scalp	T2B/T3	Tumor Diameter (2.7cm) Depth of Invasion (Galea) Large-Caliber PNI (>3 nerves)	MMS	LR In Transit Metastasis	3
8	92-year-old M	Scalp	T2B/T3	Tumor Diameter (3.8cm) Depth of Invasion (Galea) Large-Caliber PNI	MMS	LR	5

Abbreviations: S+ART, surgery and adjuvant radiation; SM, surgery monotherapy, M, male; MMS, Mohs micrographic surgery; ART, adjuvant radiation; LR, local recurrence; DM, distant metastasis; DSD, disease specific death; PNI, perineural invasion; BWH, Brigham and Women's Hospital; AJCC8, American Joint Committee on Cancer, 8th edition

Table 5. Risk factors for SM+ART cases from the matched-case analysis.

Case #	Diameter (cm)	Differentiation	Depth of Invasion	Perineural Invasion	Other Factors
1	6.2	Poor	Bone	PNI (unknown caliber)	Renal transplant recipient
2	1.7	Poor	Muscle	Possible focus of PNI	Required 3 Mohs stages to clear
3	0.4	Poor	Muscle	Multifocal smaller caliber PNI	Foci of single cell infiltration
4	4.0	Poor	Unknown	None	
5	4.2	Poor	Subcutaneous fat	PNI (unknown caliber)	CLL
6*	4.0	Moderate	Parotid	None	Renal transplant recipient
7	3.4	Poor	Subcutaneous fat/14mm	None	
8*	4.0	Well	Bone	None	
9*	1.5	Poor	Fascia	None	Lung transplant recipient LVI
10	2.4	Moderate	Parotid	PNI (unknown caliber)	Renal transplant recipient LVI
11	2.5	Poor	Muscle	None	
12	0.7	Poor	Dermis	PNI (unknown caliber)	Spindle cell histology Required 3 Mohs stages to clear
13	2.8	Poor	Subcutaneous fat/6mm	None	LVI
14	4.0	Poor	Dermis	PNI (unknown caliber)	
15	3.0	Moderate	Muscle	PNI (unknown caliber)	
16*	1.3	Poor	Dermis	Foci suspicious for PNI	Desmoplastic Single cell infiltrative
17	2.0	Well	Subcutaneous Fat	PNI (0.2mm)	
18	0.9	Well	Muscle	PNI (0.125mm)	
19	0.4	Well	Muscle	PNI (0.2mm)	Renal transplant recipient
20	3.6	Moderate	Galea	PNI (0.14mm)	
21	3.0	Poor	Subcutaneous fat	None	LVI
22	2.5	Moderate	Cartilage/5mm	None	Crohn’s disease
23	0.5	Poor	Dermis	None	No epidermal connection
24	3.6	Moderate	Cartilage	None	
25	1.0	Poor	Dermis	None	Systemic lupus erythematosus
26	3.0	Well	Subcutaneous fat	PNI (0.125mm)	
27	1.1	Well	Galea	PNI (0.08mm)	
28	3.0	Moderate	Unknown	None	CLL Close but clear margins
29	4.6	Moderate	Galea	None	
30	4.0	Poor	Bone	PNI (unknown caliber)	CLL
31	0.8	Well	Muscle	PNI (0.2mm)	

Abbreviations: PNI, perineural invasion; LVI, lymphovascular invasion; CLL, chronic lymphocytic leukemia

*Tumors that developed a poor outcome

Capsule Summary

- Radiation is sometimes used after surgery for cutaneous squamous cell carcinoma.
- Outcomes were the same with or without radiation in a matched analysis and subgroup analysis of cases with nerve invasion. Only 8% of cases recurred. All but 3 were still curable. Studies are needed determining which patients need radiation.